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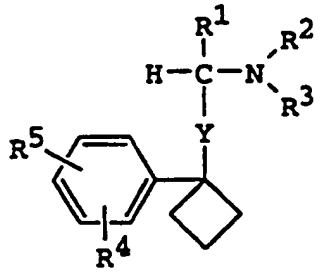
(54) Title: USE OF ARYLCYCLOBUTYLALKYLAMINES FOR THE TREATMENT OF SEIZURES AND NEUROLOGICAL DISORDERS

(57) Abstract

A method of treatment (including therapy and prophylaxis) of animals of one or more clinical conditions selected from: seizures, neurological disorders such as epilepsy and conditions in which there is neurological damage such as brain trauma, cerebral ischaemia, haemorrhage, head injuries and stroke; which comprises administering to an animal in need thereof a therapeutically and/or prophylactically effective amount of one or more compounds of formula (I), including all pharmaceutically acceptable salts thereof in which: R^1 represents C_{1-6} alkyl, pyridyl or (when Y is other than a bond) H; R^2 and R^3 independently represent H, C_{1-4} alkyl or formyl; R^4 and R^5 independently represent H, halo, phenyl, trifluoromethyl, C_{1-3} alkyl or C_{1-3} alkoxy; or if R^4 and R^5 are on adjacent carbon atoms, R^4 and R^5 together with the carbon atoms to which they are attached represent a second benzene ring, which is optionally fused to a third benzene ring; and Y represents a bond or methylene (optionally substituted with one or two C_{1-3} alkyl). A particularly preferred compound of formula (I) for administration in the above method of treatment is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine (sibutramine) especially in the form of its hydrochloride and/or hydrochloride monohydrate salts.



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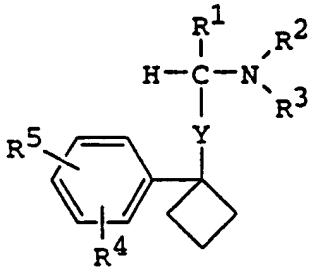
Use of arylcyclobutylalkylamines for the treatment of seizures and neurological disorders.

This invention relates to administration to an animal in need thereof of derivatives of arylcyclobutylalkylamines, and pharmaceutical compositions containing them, in a method of treatment of seizures, neurological disorders such as epilepsy and/or as conditions in which there is neurological damage such as brain trauma, cerebral ischaemia, haemorrhage, head injuries and stroke.

In particular the present invention provides a method of treatment (including therapy and prophylaxis) in animals of one or more clinical conditions selected from seizures, neurological disorders and conditions in which there is neurological damage, which comprises administering to an animal in need thereof a therapeutically or prophylactically effective amount of a compound of formula I



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including all pharmaceutically acceptable salts thereof, in which:

R^1 represents C_{1-6} alkyl, pyridyl or (when Y is other than a bond) H;

R^2 and R^3 independently represent H, C_{1-4} alkyl or formyl;

R^4 and R^5 independently represent H, halo, phenyl, trifluoromethyl, C_{1-3} alkyl or C_{1-3} alkoxy;
or if R^4 and R^5 are on adjacent carbon atoms, R^4 and R^5 together with the carbon atoms to which they are attached represent a second benzene ring, which is optionally fused to a third benzene ring; and
Y represents a bond or methylene (optionally substituted with one or two C_{1-3} alkyl).

Preferred compounds of formula I for administering in the method of treatment of present invention are those in which:
R^1 represents methyl, propyl, butyl, pentyl, pyrid-2-yl or (when Y is other than a bond) H;
R^2 represents H, methyl or formyl;
R^3 represents H or methyl;
R^4 and R^5 independently represent H, bromo, chloro, fluoro, phenyl, trifluoromethyl or methoxy;
or R^4 and R^5 together with the benzene ring to which they are attached form phenanthryl; and
Y represents a bond, methylene or dimethylmethylene.

Specific compounds of formula I for administering in the method of treatment of present invention are:

N-methyl-1-[1-(3-bromophenyl)cyclobutyl]ethylamine;
N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
N-methyl-1-[1-(4-chloro-3-trifluoromethyl)cyclobutyl-ethylamine;
N,N-dimethyl-1-[1-(3-fluoro-4-biphenylyl)cyclobutyl]-ethylamine;
1-(1-phenylcyclobutyl)-3-methylbutylamine;

N,N-dimethyl-2-[1-(4-biphenylyl)cyclobutyl]ethylamine;
1-[1-(phenylcyclobutyl)methyl]butylamine;
N,N-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropylamine;
1-[1-(2-phenanthryl)cyclobutyl]ethylamine;
N,N-dimethyl-1-[1-(3-trifluoromethylphenyl)cyclobutyl]-ethylamine;
2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine;
N-methyl-2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine;
N,N-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine;
1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]butylamine;
2-[1-(2,4-dichlorophenyl)cyclobutyl]-1-methylethylamine;
N,N-dimethyl-2-[1-(4-chloro-3-trifluoromethylphenyl)-cyclobutyl]-1-methylethylamine;
N-{1-[1-(2-fluorophenyl)cyclobutyl]butyl}formamide;
1-[1-(4-biphenylyl)cyclobutyl]-1-(2-pyridyl)methylamine;
N-[1-(1-phenylcyclobutyl)-3-methylbutyl]formamide;
3,3-dimethyl-1-(1-phenylcyclobutyl)butylamine;
1-[1-(5-chloro-2-methoxyphenyl)cyclobutyl]ethylamine;
and pharmaceutically acceptable salts thereof.

A most preferred compound for administering in the method of treatment of the present invention is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine, particularly in the form of its hydrochloride, even more particularly in the form of its hydrochloride monohydrate.

Seizures (or convulsions) result from the discharge of a large collection of neurones in abnormal synchrony and may be accompanied by loss of consciousness. They are often a symptom of some underlying clinical

condition for example one or more of the following: neurological disorders such as epilepsy and conditions in which there is neurological damage such as brain trauma, cerebral ischaemia, haemorrhage, head injuries and stroke. Seizures may also occur (particularly in children) due to one or more of the following: birth injuries, rickets, pyretus, irritation (for example bowel irritation), diseases of the brain (for example meningitis, encephalitis and/or tumours) and/or asphyxia. Seizures may be disabling particularly if chronic, and may have serious consequences. Occurrence of seizures, for example those induced by epilepsy, may be reduced or eliminated by chronic, prophylactic drug treatment, although this may not cure the underlying clinical condition. The most common cause of seizures in adults is epilepsy which occurs in about one percent of the general population. Many epileptics find currently available anti-convulsants are not effective in controlling their seizures. Currently available anti-convulsants also have undesirable side effects, particularly if used chronically. Such side effects include drowsiness, dose dependent side effects and/or rare allergic and/or idiosyncratic reactions.

Therefore it would be desirable to provide a method of treatment which is more potent than known treatments against seizures and/or underlying clinical conditions that may cause seizures and/or does not have some or all of the disadvantages described herein for known treatments.

Certain compounds of formula I are described in British Patent Specification 2098602A. A preferred compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine (also known by the non- proprietary name of sibutramine). The use

of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of depression is described in British Patent Specification 2098602 A; the use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of Parkinson's disease is described in international patent application WO 88/06444; and the use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of obesity is described in international patent application WO 90/06110. The particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in European Patent Application 0230742 A. The remaining compounds described herein have been disclosed in GB 2128991.

It will be understood by persons skilled in the art that a substituent group which comprises three or more atoms signifies a group which may comprise a straight chain or a group which is branched, for example, an alkyl group may comprise propyl which includes n-propyl and isopropyl, butyl which includes n-butyl, sec-butyl, isobutyl and tert-butyl. The total number of certain atoms is specified herein for certain substituents, for example C_{1-6} alkyl signifies an alkyl group having from 1 to 6 carbon atoms. The term 'halo' as used herein signifies fluoro, chloro, bromo and iodo. If ring substituents (for example R^4 and R^5) are other than H, the substituents may replace any H attached to an atom in the ring and may be located at any available position on the ring.

Certain compounds of formula I may form salts of formula I with organic and/or inorganic acids (for

example acid addition salts). Particularly suitable salts of formula I which are pharmaceutically acceptable and which may be formed with acids comprise salts of acidic amino acids and/or suitable derivatives thereof (for example salts of glutamic acids and/or N-carbamoyl-phenylalanine), salts of suitable inorganic acids (for example salts of hydrobromic, hydrochloric, hydriodic, nitric, phosphoric, sulphonic and/or sulphuric acids) and/or salts of suitable organic acids (for example salts of acetic, alkylsulphonic, alkylsulphuric, arylsulphonic, arylsulphuric, ascorbic, benzoic, cinnamic, citric, dibenozyltartaric, dodecanoic, fumaric, gluconic, glycollic, isothionic, lactobionic, lactic, maleic, malic, mandelic, palmitic, pamoic, pyruvic, salicylic, succinic and/or tartaric acids and/or suitable derivatives thereof). Salts of formula I include all pharmaceutically acceptable salts that may be formed from multivalent acids (for example acid metal salts [such as bicarbonate and/or hydrogen orthophosphate salts]) and all enantiomeric salts formed with pharmaceutically acceptable chiral acids and/or any mixtures of enantiomers of such salts (for example (+) tartrates and/or (-) tartrates). Salts of formula I may be prepared by reacting corresponding compounds of formula I which are not salts with suitable acids in a conventional manner. The method of treatment of the present invention includes administering of all pharmaceutically acceptable salts of formula I and/or any mixtures thereof. Particularly preferred salts of formula I are the monohydrochloride, dihydrochloride and maleate salts.

Certain compounds of formula I may have a structure such that they are not superimposable on their mirror image (for example compounds of formula I with one or more chiral centres) and thus exist as different

enantiomeric forms which may or may not be optically active. Thus, for example, if R^1 is other than H, compounds of formula I contain a chiral centre at the asymmetrically substituted carbon atom to which R^1 is attached. Compounds of formula I that contain a single chiral centre exist as two enantiomeric forms. The method of treatment of the present invention includes administering all pharmaceutically acceptable, enantiomerically pure enantiomers of compounds of formula I and/or any mixtures of such enantiomers (for example racemic mixtures).

Enantiomers may be obtained by methods known to those skilled in the art. Such methods typically include one or more of any of the following:

resolution via formulation of diastereoisomeric salts and/or complexes which may be separated, for example, by crystallisation;

formation of diasterseoisomeric derivatives and/or complexes which may be separated (for example, by crystallisation, gas-liquid chromatography and/or liquid chromatography), followed by the liberation of the desired enantiomer from the separated derivative;

selective reaction of one enantiomer using an enantiomer-specific reagent followed by separation of the modified and/or unmodified enantiomers;

biochemical methods (for example fermentation with living organisms such as moulds, yeasts and/or bacteria [optionally such organisms being genetically modified] and/or enzymatic modification [such as esterification, oxidation and/or reduction]);

gas-liquid chromatography and/or liquid chromatography in a chiral environment (for example on a chiral support [such as silica gel with a bound chiral ligand] and/or in the presence of a chiral solvent);

asymmetric synthesis of a specific enantiomer (for example using optically active reagents, substrates, catalysts, solvents and/or enzymatic processes);
asymmetric transformation (for example by asymmetric synthesis, asymmetric destruction and/or asymmetric kinetic resolution) of one enantiomer into another; and/or
by any other suitable method (for example separation of visually distinguishable chiral crystals, selective crystallisation of one enantiomer using a chiral seed crystal and/or induction of a photochemical reaction using circularly polarized electromagnetic radiation).

Certain compounds of formula I may contain two or more chiral centres and thus may exist as one or more diastereoisomeric pairs. Diastereoisomers may be separated by methods known to those skilled in the art, for example by chromatography and/or crystallisation and individual enantiomers within the diastereoisomers may be separated as described above. The method of treatment of present invention includes administering all pharmaceutically acceptable diastereoisomers of compounds of formula I and/or any mixtures thereof.

It will be appreciated that where the active moiety is transformed by the separation procedures described above, a further step may be required to convert the transformation product back to the active moiety.

Compounds of formula I may exist as solvates (for example if the solvent is water the hydrates may be hemihydrates, monohydrates and/or dihydrates) or as an unsolvated form (for example an anhydrous form). The degree of solvation may also be non-stoichiometric. The method of treatment of present invention includes administering of all pharmaceutically acceptable

solvates of compounds of formula I and/or any mixtures thereof. A particularly preferred solvate of compounds of formula I is the monohydrate.

As used herein, in the singular or plural, the term 'Active Compound' denotes one or more compound or compounds of formula I (comprising any of the different forms described herein) and/or any mixtures thereof. Conveniently the Active Compound comprises the preferred and/or particularly preferred compounds of formula I described herein. Specific compounds which may comprise the Active Compound are the compounds specifically mentioned herein which have been shown to be active in the pharmacological tests described herein.

As used herein, in the singular or plural, the term 'Pharmaceutical Composition' denotes one or more pharmaceutical compositions and/or any mixtures thereof comprising a therapeutically and/or prophylactically effective amount of one or more compounds of formula I (comprising any of the different forms described herein) and/or any mixtures thereof, in conjunction with any pharmaceutically acceptable diluent and/or carrier (for example those described herein). Conveniently the Pharmaceutical Composition comprises the preferred and/or particularly preferred compounds of formula I described herein. Specific compounds which may be incorporated into the Pharmaceutical Composition are those compounds of formula I which have been shown to be active in the pharmacological tests described herein.

The most suitable route for administering the Active Compound depends on many factors (for example the particular clinical condition treated, its severity and/or the specific compound used). Preferably, in the treatments described herein, the Active Compound may be

administered orally, rectally, parenterally, nasally, bucally and/or topically; more preferably orally. Thus Pharmaceutical Composition suitable for use in the methods of treatment of the present invention may take the form of any pharmaceutical compositions suitable for such methods of administration (for example one or more of the Pharmaceutical Compositions described herein and/or any mixtures thereof). Generally Pharmaceutical Compositions will be accompanied by written and/or printed directions for their use and/or administration in the method of treatment of the present invention.

Pharmaceutical Compositions may be prepared by any method known to those skilled in the art, for example by bringing the Active Compound into association with suitable inert diluents, carriers and/or any other optional ingredients (for example those described herein). The ingredients of the Pharmaceutical Composition may be uniformly and/or intimately admixed and the resultant Pharmaceutical Composition may be shaped (for example by compressing and/or moulding). It will be appreciated by those skilled in the art that if the Pharmaceutical Composition contains large amounts of excipients in relation to the Active Compound, repeated conventional mixing operations may be required to distribute the Active Compound evenly and/or homogenously throughout the Pharmaceutical Composition. Pharmaceutical Compositions may also be formulated in a manner known to those skilled in the art, to give a modified release (for example rapid, delayed, sustained and/or controlled release) of the Active Compound. Pharmaceutically acceptable diluents and/or carriers suitable for use in Pharmaceutical Compositions are well known in the art of pharmacy. The excipients used in the preparation of Pharmaceutical Compositions are the excipients known in the pharmacist's art.

Pharmaceutical Compositions may be administered orally in known pharmaceutical forms for such administration which may be solid or fluid. Dosage forms suitable for oral administration may comprise cachets, caplets, capsules, dragées, elixirs, extrudates, granules, lozenges, pastilles, pills, pellets, powders, solutions, suspensions, syrups, tablets and/or troches.

Solid oral dosage forms may be prepared by mixing the Active Compound with one or more of the following ingredients which are pharmaceutically acceptable: inert diluents, disintegrating agents, lubricants, binders and or any mixtures thereof. It will be appreciated by those skilled in the art that a particular ingredient may perform more than one function (for example maize starch may act as a diluent, binder and/or disintegrating agent).

Inert diluents may comprise sugars (for example lactose, fructose, sucrose, powdered sugar and/or mixtures thereof), sugar alcohols (for example mannitol), celluloses (for example microcrystalline cellulose), starches (for example maize starch, other pharmaceutical grade starch and/or mixtures thereof), dextrin, clays (for example kaolin), inorganic material (for example calcium phosphate, calcium sulphate and/or sodium chloride) and/or mixtures thereof.

Disintegrating agents may comprise starches (for example maize starch, sodium starch glycolate and/or mixtures thereof), agar, bentonite, celluloses (for example methyl cellulose, carboxymethylcellulose, microcrystalline cellulose, hydroxypropyl cellulose and/or mixtures thereof), alginic acid, alginate salts,

guar gum, croscarmellose sodium, sodium lauryl sulphate, colloidal silicon dioxide and/or mixtures thereof.

Lubricating agents may comprise stearic acid, stearates (for example magnesium stearate, calcium stearate and/or glyceryl palmtostearate), talc, polyethylene glycol, glyceryl behenate and/or mixtures thereof.

Binders may comprise starches (for example maize starch), gelatin, sugars (for example sucrose, molasses, lactose and/or mixtures thereof) and/or natural and/or synthetic gums (for example acacia, sodium alginate, extract of Irish moss, celluloses [such as carboxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose, ethylcellulose, micro-crystalline cellulose and/or mixtures thereof], polyethylene glycol, waxes, polyvinylpyrrolidone and/or mixtures thereof).

Solid oral dosage forms of the present invention may further comprise one or more of the following ingredients and/or mixtures thereof:

colouring agents (for example conventional pharmaceutically acceptable and/or food desirable dyes and/or colorants);

sweetening agents (for example intense sweeteners [such as aspartame and/or saccharin]);

flavouring agents (for example pharmaceutically acceptable and/or food desirable flavours);

anti-microbial agents (for example methyl p-hydroxybenzoate, propyl p-hydroxybenzoate-sodium benzoate, sodium propionate and/or sorbic acid);

anti-oxidants (for example ascorbic acid, sodium ascorbate, sodium metabisulphate and/or propyl gallate);

wetting agents (for example sodium lauryl sulphate); and/or

one or more pharmaceutically acceptable couples (for example those comprising an acid and a carbonate and/or bicarbonate salt), which effervesce to aid dissolution if the solid dosage form is added to water.

Solid dosage forms of the present invention may also optionally comprise one or more other pharmaceutically acceptable ingredients and/or mixtures thereof, which are known in the art to permit production of oral dosage forms by known methods (for example blending, filling and/or tabletting). Such ingredients may comprise:

agents to aid the flow of ingredients (for example talc and/or colloidal silicon dioxide);

compression agents to increase the strength of the solid dosage form (for example sorbitol and/or lactose); and/or

ionic and/or non-ionic surface active agents (for example sodium lauryl sulphate) to disperse the Active Compound within the solid dosage form and prevent grit forming at the surface of the solid dosage form. Preferably solid oral dosage forms are shaped to be more convenient for general use.

Solid oral dosage forms may be formulated in a manner known to those skilled in the art so as to give a sustained release of the Active Compound. Enteric coated, solid oral dosage forms comprising Pharmaceutical Compositions may be advantageous, depending on the nature of the Active Compound. Various materials, for example shellac and/or sugar, may be present as coatings, or to otherwise modify the physical form of the oral dosage form. For example tablets and/or pills may, if desired, be provided with enteric coatings (such as membranes) by known methods, for example by the use of cellulose acetate phthalate,

polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and/or anionic polymers of methacrylic acid and/or its esters. To prevent and/or reduce cracking of the enteric coating during its application and/or storage of the solid dosage form, the enteric coating may comprise a plasticiser (for example diethyl phthalate, tributyl citrate and/or triacetin). Capsules and/or caplets (for example hard or soft gelatin capsules) comprising the Active Compound (with or without added excipients [such as a fatty oil]), may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The contents of capsules and/or caplets may be formulated using known methods to give sustained release of the Active Compound.

The Active Compound may be formulated into granules and/or powders with or without additional excipients. The granules and/or powders may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules and/or powders may contain disintegrants (for example pharmaceutically acceptable effervescent couples formed from acids and carbonate and/or bicarbonate salts) to facilitate dispersion in liquid media.

Fluid oral dosage forms comprising the Pharmaceutical Compositions are preferably liquid oral dosage forms and may be elixirs, solutions, syrups and/or suspensions which contain the Active Compound in pharmaceutically acceptable media. Pharmaceutically acceptable solvents comprise water, glycol, oils and/or alcohols. Media suitable for preparing syrups and/or suspensions may comprise aqueous media, oily media and/or emulsions in the presence of one or more pharmaceutically acceptable suspending agents (for

example starches, gums [such as xanthan gum], celluloses [such as methylcellulose, hydroxyethyl-cellulose and/or sodium carboxymethylcellulose], gelatin, glycerin, hydrogenated fats and/or sorbitol). Suitable oily media may comprise vegetable oils (for example arachis oil and/or sunflower oil), other edible oils (for example almond oil and/or fractionated coconut oil) and/or oily esters (for example esters of glycerin, propylene glycol and/or ethanol). Fluid oral dosage forms may further comprise one or more of the following which are pharmaceutically acceptable: agents which vary osmotic pressure (for example salts), colouring agents, emulsifiers (for example lecithin, sorbitan monooleate and/or acacia), flavouring agents, pH adjusting agents (for example buffers), preservatives, sweetening agents and/or mixtures thereof. Fluid oral dosage forms may also be prepared from dry products (for example granules and/or powders) which are presented for reconstitution with a suitable vehicle (for example those media described above).

Pharmaceutical Compositions may be administered rectally in the known pharmaceutical forms for such administration (for example suppositories with a base comprising sugars, starches, stearates, hard fats, semi-synthetic glycerides, cocoa butter, polyethylene glycols and/or any mixtures thereof).

Pharmaceutical Compositions may also be administered parenterally (for example subcutaneously, intramuscularly, intradermally and/or intravenously [such as by injection and/or infusion]) in the known pharmaceutical dosage forms for parenteral administration (for example sterile suspensions in aqueous and/or oily media and/or sterile solutions in suitable solvents, preferably isotonic with the blood of

the intended patient). Parenteral dosage forms may be sterilised (for example by micro-filtration and/or using suitable sterilising agents [such as ethylene oxide]). Optionally one or more of the following pharmaceutically acceptable adjuvants suitable for parenteral administration may be added to parenteral dosage forms: local anaesthetics, preservatives, buffering agents and/or mixtures thereof. Parenteral dosage forms may be stored in suitable sterile sealed containers (for example ampoules and/or vials) until use. To enhance stability during storage the parenteral dosage form may be frozen after filling the container and fluid (for example water) may be removed under reduced pressure.

Pharmaceutical compositions may be administered nasally in known pharmaceutical forms for such administration (for example sprays, aerosols, nebulised solutions and/or powders). Metered dose systems known to those skilled in the art (for example aerosols and/or inhalers) may be used.

Pharmaceutical compositions may be administered to the buccal cavity (for example sub-lingually) in known pharmaceutical forms for such administration (for example slow dissolving tablets, chewing gums, troches, lozenges, pastilles, gels, pastes, mouthwashes, rinses and/or powders).

Pharmaceutical compositions may be administered topically in forms suitable for topical administration (hereinafter known as Topical Compositions). The amount of Active Compound in a Topical Composition should be such that a therapeutically and/or prophylactically effective amount of the Active Compound would be delivered during the period of time which the Topical Composition is intended to be on the skin.

Topical vehicles suitable for use in the Topical Compositions may comprise pharmaceutically acceptable foam, paste, salve, lotion, cream, ointment, oil, emulsion and/or gel bases; and/or compositions suitable for application as a spray and/or aerosol. Topical vehicles may also comprise topical delivery devices such as cataplasms, poultices, patches and/or impregnated bandages.

Topical Compositions may comprise a matrix in which the Active Compound is administered transdermally by being held in contact with the skin. The Active Compound may also be delivered transdermally from a suitable Topical Composition by electrotransport and/or iontophoresis. Topical Compositions suitable for transdermal administration may further comprise the Active Compound optionally held in an aqueous solution which may be dissolved and/or dispersed in an adhesive and/or polymer base (for example on a patch). Suitable transdermal Topical Compositions may also be prepared by mixing and/or dispersing the Active Compound in topical vehicles together with potential transdermal accelerants (such as dimethyl sulphoxide and/or propylene glycol).

Suitable creams may be prepared by incorporating the active compound in petroleum and/or light liquid paraffins which are then dispersed in aqueous media using surfactants. Ointments may be prepared by mixing the active compound with mineral oils, petrolatum and/or waxes (for example paraffin wax and/or beeswax). Gels may be prepared by mixing the active compound with gelling agents (for example those described below) in the presence of water and/or optionally a base. Clear gels may comprise clarifying agents (for example denaturated alcohols [such as denaturated ethanol]).

Topical Compositions that comprise emulsions may comprise either oil-in-water or water-in-oil emulsions. The oil phase of such emulsions may comprise one or more of the following ingredients: hydrocarbon oils, waxes, natural oils, silicone oils, fatty acid esters, fatty alcohols and/or any mixtures thereof. Pharmaceutical Compositions that are emulsions may be prepared using emulsifiers suitable for use in water-in-oil and/or oil-in-water emulsions and preferably acceptable for use in Topical Compositions. Such emulsifiers may comprise any suitable emulsifiers well known to those skilled in the art.

Topical Compositions may also comprise ionic or non-ionic surface active agents to promote greater therapeutic and/or prophylactic activity in the Topical Compositions if applied topically. The surface active agents may also comprise emulsifying ingredients and/or surfactants even if the Topical Compositions are other than emulsions.

Topical Compositions may additionally comprise further components well known to those skilled in the art and/or any mixtures thereof, for example: emulsion stabilisers, sequestrants, emollients, humectants, moisturisers, thickening agents, gelling agents, film formers, perfumes, anti-oxidants, preservatives, colouring agents and/or mixtures thereof.

Topical Compositions may further comprise pH adjusting agents. Preferably, the pH adjusting agents are present in an amount which is sufficient to activate the thickening and/or gelling agents, if present, and which will keep the pH of the Topical Composition within pharmaceutically and cosmetically acceptable limits that will not damage the skin. More preferably the pH of the

Topical Composition is from about 5.0 to about 9.0. Subject to the aforementioned, the pH adjusting agents may comprise sodium citrate, sodium hydroxide, potassium hydroxide, and/or N,N,N'N'-tetrakis(2-hydroxypropyl)-ethylenediamine (available commercially under the trade name Quadrol).

Active Compounds may also be administered by continuous infusion either from an external source (for example by intravenous infusion) and/or from a source of the Active Compound placed within the body. Internal sources include implants and/or implanted reservoirs containing the Active Compound to be infused from which the Active Compound is continuously released (for example by osmosis). Liquid implants may comprise suspensions and/or solutions in a pharmaceutically acceptable solvent of the Active Compound to be infused (for example as oily solutions of oils of very sparingly water-soluble derivatives of the Active Compound such as dodecanoate salts). Solid implants may be in the form of an implanted support (for example synthetic resins and/or waxy materials) for the Active Compound to be infused. The support may be a single body containing all the Active Compound or a series of several bodies each containing part of the Active Compound to be delivered. The amount of Active Compound present in an internal source should be such that a therapeutically and/or prophylactically effective amount of the Active Compound is delivered over a long period of time.

Active Compounds that have a high lipid solubility may be suitable for use in so-called depot formulations which provide a source of the Active Compound located within the body (for example by intra-muscular injection). Depot formulations may comprise the Active Compound in a pharmaceutically acceptable oil.

In some formulations it may be beneficial to use the Active Compound and/or the Pharmaceutical Composition in the form of particles of very small size, for example as obtained by fluid energy milling. Alternatively the Active Compound may be bound (for example by sorption, incorporation and/or chemically) to nanoparticles which are colloidal polymeric particles of a size typically less than 1 micron. The distribution of such nanoparticles in the body and hence the sites of delivery of the Active Compound can be effected by coating the surface of the nanoparticles appropriately (for example with surfactants and/or antibodies).

In the Pharmaceutical Composition the Active Compound may, if desired, be associated with other compatible, pharmacologically active ingredients.

The Active Compound and/or the Pharmaceutical Composition is indicated for therapeutic and/or prophylactic use as a medicament for the treatment in animals of one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage. Specific clinical conditions for which the Active Compound and/or the Pharmaceutical Composition are indicated comprise brain trauma, cerebral ischaemia, epilepsy, haemorrhage, head injuries and stroke.

The therapeutic and/or prophylactic activity of compounds falling within the disclosure of formula I has been demonstrated by means of various pharmacological tests such as in vitro tests and in vivo tests in standard laboratory animals. Such tests include the test of pharmacological activity described herein.

Therefore the present invention provides a method of treatment in animals of one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage, which comprises administering to a patient in need thereof a therapeutically and/or prophylactically effective amount of the Active Compound and/or the Pharmaceutical Composition.

It will be appreciated that the term 'treatment' as used herein includes both therapeutic and/or prophylactic use of the Active Compound and/or the Pharmaceutical Composition. The Active Compound and/or the Pharmaceutical Composition may be used to provide a systemic therapeutic and/or prophylactic effect. In the present invention prophylactic use of the Active Compound and/or the Pharmaceutical Composition comprises administering to an animal in need thereof the Active Compound and/or the Pharmaceutical Composition to prevent of the onset of one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage; and/or use of the Active Compound and/or the Pharmaceutical Composition as a neuroprotective agent to protect an animal against one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage.

Animals that may be treated according to the present invention comprise human beings as well as non-human animals. As used herein the term 'animal' comprises both humans and non-human animals. Non-human animals that may be so treated comprise any animal (including non-mammals) that has any of the clinical conditions described herein. Preferably the animals treated according to the invention are mammals (for

example the animal species tested as described herein), more preferably human beings.

While the precise mechanism of action of the Active Compound is unknown at present, it is believed that at least some of the pharmacological effects of the Active Compound and/or the Pharmaceutical Composition in the clinical conditions described herein may arise from activity blocking one or more voltage-dependent sodium ion (Na^+) channels in neurones, potentiating the transmission of the neurotransmitter gamma-amino butyric acid (GABA), attenuating the transmission of the excitatory amino acids (for example glutamic and/or aspartic) and activating one or more potassium ion (K^+) and/or calcium ion (Ca^{2+}) channels in neurones (for example voltage dependant K_A channels and/or calcium ion [Ca^{2+}] activated SK_{Ca} channels). Consequently, another aspect of the present invention is a method of treatment as described herein in which the Active Compound and/or the Pharmaceutical Composition administered has activity blocking one or more voltage-dependent sodium ion (Na^+) channels in neurones, potentiating the transmission of the neurotransmitter gamma-amino butyric acid (GABA), inhibiting excitatory amino acid neurotransmission, activating one or more potassium ion (K^+) channels in neurones and activating one or more calcium (Ca^{2+}) channels in neurones. However, the method of treatment of the present invention should not be considered limited to administering those Active Compounds and/or those Pharmaceutical Compositions having such pharmacological activity.

The precise amount of the Active Compound administered to a particular animal, preferably a mammal, more preferably a human being, in the method of treatment of the present invention will depend on a

number of factors (for example: the specific compound administered, its mode of administration and/or the use for which it is intended; the particular clinical condition being treated and/or its severity; and/or the age, body mass and/or past clinical history of the patient to be treated) and always lies within the sound discretion of the person administering and/or supervising the treatment (for example a medical practitioner [such as nurse and/or physician] and/or veterinarian). Nevertheless, a suitable daily dose of the Active Compound for administration to an animal is generally from about 0.01mg/day per kg of the animal's body mass to about 10mg/kg/day given in a single dose and/or in divided doses at one or more times during the day. The total dose of the Active Compound administered per day may be generally from about 0.1mg to about 500mg. The Pharmaceutical Composition may contain from about 0.1% to about 99% by weight of the Active Compound and is generally prepared in unit dose form, a unit dose of Active Compound generally being from about 0.1mg to about 500mg. If the Active Compound is a salt the masses indicated above refer to the mass of the corresponding Active Compound that is other than a salt.

A further aspect of the present invention provides the use of the Active Compound and/or the Pharmaceutical Composition in the manufacture of a medicament for the treatment in animals of one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage.

A yet further aspect of the present invention provides use of the Active Compound and/or the Pharmaceutical Composition for treating in animals in need thereof, one or more clinical conditions selected

from: seizures, neurological disorders and conditions in which there is neurological damage.

A still further aspect of the present invention provides a pharmaceutical composition for treating in animals one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage; comprising a therapeutically and/or prophylactically effective amount of the Active Compound in conjunction with a pharmaceutically acceptable diluent or carrier.

The pharmacological activity of compounds of formula I in the methods of the present invention was demonstrated by activity of certain compounds of formula I (those compounds so tested referred to hereinafter as 'Test Compounds') in the following pharmacological test: the inhibition of seizures induced by maximal electroshock (referred to hereinafter as the MESM Test).

Inhibition of seizures induced by maximal electroshock (MESM Test)

This test of anticonvulsant activity involved observing the ability of Test Compounds to inhibit seizures in mice induced by a maximal electroshock (see Loscher W. and Schmidt D.; Epilepsy Res.; 1988; 2; 145-181).

In the MESM experiments, groups of male mice in the weight range 25 to 30 grammes had free access to food and water until the start of the experiment. The mice were divided into two groups, a control group and a test group to which Test Compounds would be administered. The control group received an oral dose of 10 ml/kg of a

vehicle of 1% aqueous methylcellulose solution. The test group received orally, suspended in the same dose of the methylceullose vehicle, a Test Compound at a dose of either 100 mg/kg for initial testing or, if enough Test Compound was available, at a range of doses to determine an ED_{50} (see below). One hour after administration of all drugs an electroshock of duration 1.0 second was administered to all mice in both groups through ear clip electrodes moistened with saline. The electroshock had an intensity of 99mA, frequency of 50 Hz and pulse width of 0.4 ms. Such a shock would generally be expected to induce a seizure in the mice.

During the following two minutes the mice in each group were observed, the number of mice in each group exhibiting tonic hind limb extension was recorded and thus the percentage of mice in which seizures had been inhibited was determined. The greater the anticonvulsant activity of the Test Compound, the higher was the percentage recorded in the MESM test. Test Compounds with a percentage inhibition of greater than or equal to 50% were deemed to be active in the MESM Test.

If results at more than one dose were available, then a value for the dose inhibiting seizures in 50% of the mice (ED_{50}) was calculated from the regression straight line plot of the percentage of mice in which seizures were inhibited against the $\log_{10}$ (dose) of the Test Compound administered.

The data obtained from the MESM Test for certain compounds of formula I are tabulated below. In the table 'A' indicates the compound satisfied the criteria for activity in the MESM Test but no quantitative data were available.

Table

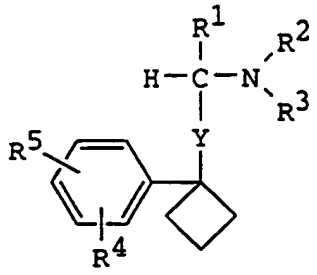
Ex. No.	Name	MESM/Activity as % protection (%) or ED_{50} (mg/kg)
1	N-methyl-1-[1-(3-bromophenyl)cyclobutyl]ethylamine	100%
2	N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine	32.7mg/kg
3	1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine	33.0mg/kg
4	N,N-dimethyl-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine	49.7mg/kg
5	N-methyl-1-[1-(4-chloro-3-trifluoromethyl)-cyclobutylethylamine	28.9mg/kg
6	N,N-dimethyl-1-[1-(3-fluoro-4-biphenylyl)-cyclobutyl]ethylamine	16.2mg/kg
7	1-(1-phenylcyclobutyl)-3-methylbutylamine	22.0mg/kg
8	N,N-dimethyl-2-[1-(4-biphenylyl)cyclobutyl]ethylamine	35.9mg/kg
9	1-[1-(phenylcyclobutyl)methyl]butylamine	81mg/kg
10	N,N-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropylamine	A
11	1-[1-(2-phenanthryl)cyclobutyl]ethylamine	18.9mg/kg
12	N,N-dimethyl-1-[1-(3-trifluoromethylphenyl)cyclo-butyl]ethylamine	70%

Ex. No.	Name	MESM/Activity as % protection (%) or ED_{50} (mg/kg)
13	2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethyl-propylamine	71.3mg/kg
14	N-methyl-2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine	47mg/kg
15	N,N-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine	47.9mg/kg
16	1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]butylamine	90%
17	2-[1-(2,4-dichlorophenyl)cyclobutyl]-1-methylethylamine	65.8mg/kg
18	N,N-dimethyl-2-[1-(4-chloro-3-trifluoromethyl-phenyl)cyclobutyl]-1-methylethylamine	90%
19	N-{1-[1-(2-fluorophenyl)cyclobutyl]butyl}formamide	42.3mg/kg
20	1-[1-(4-biphenylyl)cyclobutyl]-1-(2-pyridyl)methylamine	90%
21	N-{1-(1-phenylcyclobutyl)-3-methyl-butyl}formamide	48.7mg/kg
22	3,3-dimethyl-1-(1-phenylcyclobutyl)butylamine	55.7mg/kg
23	1-[1-(5-chloro-2-methoxyphenyl)cyclobutyl]ethylamine	70%

Examples 1, 2, 3, 4, 5, 7, 11 and 16 herein have been exemplified in the applicant's British patent GB 2098602 (corresponding to examples 4d, 9c, 10c, 11, 4h, 10h, 10y and 10r respectively) and can be prepared as described therein. Examples 6, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 21, 22 and 23 are disclosed generally in GB 2098602A and processes for their preparation are disclosed generally therein. Example 20 is disclosed generally in GB 212899A and processes for its preparation are described generally therein.

Claims

1. A method of treatment in animals of one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage, which comprises administering to an animal in need thereof, a therapeutically or prophylactically effective amount of one or more compounds of formula I



I

including all pharmaceutically acceptable salts thereof in which:

R^1 represents C_{1-6} alkyl, pyridyl or (when Y is other than a bond) H;

R^2 and R^3 independently represent H, C_{1-4} alkyl or formyl;

R^4 and R^5 independently represent H, halo, phenyl, trifluoromethyl, C_{1-3} alkyl or C_{1-3} alkoxy;
or if R^4 and R^5 are on adjacent carbon atoms, R^4 and R^5 together with the carbon atoms to which they are attached represent a second benzene ring, which is optionally fused to a third benzene ring; and

Y represents a bond or methylene (optionally substituted with one or two C_{1-3} alkyl).

2. A method of treatment as claimed in claim 1, comprising administering one or more compounds of formula I, in which:

R^1 represents methyl, propyl, butyl, pentyl, pyrid-2-yl or (when Y is other than a bond) H;

R^2 represents H, methyl or formyl;

R^3 represents H or methyl;

R^4 and R^5 independently represent H, bromo, chloro, fluoro, phenyl, trifluoromethyl or methoxy;

or R^4 and R^5 together with the benzene ring to which they are attached form phenanthryl; and

Y represents a bond, methylene or dimethylmethylene.

3. A method of treatment as claimed in any preceding claim, comprising administering one or more compounds of formula I selected from:

N-methyl-1-[1-(3-bromophenyl)cyclobutyl]ethylamine;

N-methyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;

1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;

N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;

N-methyl-1-[1-(4-chloro-3-trifluoromethyl)cyclobutyl-ethylamine;

N,N-dimethyl-1-[1-(3-fluoro-4-biphenylyl)cyclobutyl]-ethylamine;

1-(1-phenylcyclobutyl)-3-methylbutylamine;

N,N-dimethyl-2-[1-(4-biphenylyl)cyclobutyl]ethylamine;

1-[1-(phenylcyclobutyl)methyl]butylamine;

N,N-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-2-methylpropylamine;

1-[1-(2-phenanthryl)cyclobutyl]ethylamine;

N,N-dimethyl-1-[1-(3-trifluoromethylphenyl)cyclobutyl]-ethylamine;

2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine;
N-methyl-2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine;
N,N-dimethyl-2-[1-(4-chlorophenyl)cyclobutyl]-1,2-dimethylpropylamine;
1-[1-(4-chloro-3-fluorophenyl)cyclobutyl]butylamine;
2-[1-(2,4-dichlorophenyl)cyclobutyl]-1-methylethylamine;
N,N-dimethyl-2-[1-(4-chloro-3-trifluoromethylphenyl)-cyclobutyl]-1-methylethylamine;
N-{1-[1-(2-fluorophenyl)cyclobutyl]butyl}formamide;
1-[1-(4-biphenylyl)cyclobutyl]-1-(2-pyridyl)methylamine;
N-[1-(1-phenylcyclobutyl)-3-methylbutyl]formamide;
3,3-dimethyl-1-(1-phenylcyclobutyl)butylamine;
1-[1-(5-chloro-2-methoxyphenyl)cyclobutyl]ethylamine;
and pharmaceutically acceptable salts thereof.

4. A method of treatment as claimed in any preceding claim, in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

5. A method of treatment as claimed in any preceding claim, in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

6. A method of treatment as claimed in any preceding claim, comprising administering one or more compounds of formula I which have activity selected from one or more of: blocking one or more voltage-dependent sodium ion (Na^+) channels in neurones, potentiating the transmission of the neurotransmitter gamma-amino butyric acid (GABA), attenuating the transmission of excitatory amino acids, activating one or more potassium ion (K^+)

channels in neurones and activating one or more calcium ion (Ca^{2+}) channels in neurones.

7. A method of treatment as claimed in any preceding claim, in which the clinical condition to be treated is selected from: brain trauma, cerebral ischaemia, epilepsy, haemorrhage, head injuries and stroke

8. A method of treatment as claimed in any preceding claim, in which the animal treated comprises a human being.

9. The use of a compound of formula I as represented in any of claims 1 to 5 in the manufacture of a medicament for the treatment of one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage.

10. The use as claimed in claim 9, of a compound of formula I as represented in any of claims 1 to 5, in which the medicament is for the treatment of one or more clinical conditions selected from: brain trauma, cerebral ischaemia, epilepsy, haemorrhage, head injuries and stroke.

11. The use as claimed in either claim 9 or 10, of a compound of formula I as represented in any of claims 1 to 5, in which the medicament is for the treatment of human beings.

12. The use of a compound of formula I as presented in any of claims 1 to 5, optionally in conjunction with a pharmaceutically acceptable diluent or carrier, in a method of treatment of one or more clinical conditions

selected from: seizures, neurological disorders and conditions in which there is neurological damage.

13. The use as claimed in claim 12, of a compound of formula I as represented in any of claims 1 to 5, in which the clinical condition is selected from: brain trauma, cerebral ischaemia, epilepsy, haemorrhage, head injuries and stroke.

14. The use as claimed in either claim 12 or 13, of a compound of formula I as represented in any of claims 1 to 5, in which the animal to be treated is a human being.

15. A pharmaceutical composition for treating in animals one or more clinical conditions selected from: seizures, neurological disorders and conditions in which there is neurological damage, comprising a therapeutically or prophylactically effective amount of a compound of formula I as represented in any of claims 1 to 5, in conjunction with a pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition as claimed in claim 15, for treating one or more clinical conditions selected from: brain trauma, cerebral ischaemia, epilepsy, haemorrhage, head injuries and stroke.

17. A pharmaceutical composition as claimed in either claim 15 or 16, for treating humans.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/00440

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 339 280 (THE BOOTS CO.) 2 November 1989 see page 2, line 1 - page 4, line 15	1-17
X	WO,A,94 00114 (SEPRACOR) 6 January 1994 see page 4, line 11 - page 7, line 20	1-17
A	US,A,3 526 656 (BUTLER ET AL.) 1 September 1970 see column 3, line 39 - line 70	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 1995	31. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gerli, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 95/00440

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PSYCHOPHARMACOLOGY, vol. 107,no. 4, 1992 pages 497-502, 'A comparison of various antidepressant drugs demonstrates a rapid desensitisation of alpha-2 adrenoceptors exclusively by sibutramine hydrochloride' see page 498, left column, paragraph 2 see page 501, left column, line 51 - line 56 -----	1-17

1

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/EP 95/00440

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-8 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati· Application No
PCT/EP 95/00440

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-339280	02-11-89	JP-A-	1250315	05-10-89
		US-A-	4939175	03-07-90
WO-A-9400114	06-01-94	AU-B-	4542893	24-01-94
		CA-A-	2138998	06-01-94
		EP-A-	0647134	12-04-95
US-A-3526656	01-09-70	NONE		